thalidomide, which has no activity in classical immune complex disorders, or the fact that immune complexes could not be consistently detected in patients with erythema nodosum leprosum. In 1987, we reported that cyclosporine, a specific inhibitor of interleukin-2 activity, was effective in controlling recalcitrant cases of erythema nodosum leprosum.[4] More recently it has been shown that levels of tumor necrosis factor-α (TNFα) are elevated in patients with this reaction and that thalidomide acts by selectively inhibiting TNFα.[5] If this finding is confirmed, there is a strong possibility that one or more of the anti-TNF agents currently under development will provide a therapeutic alternative for erythema nodosum leprosum without the toxicity of thalidomide or cyclosporine.

Despite these dramatic developments, there remain several areas of concern or where further research is needed. It is critical that existing control programs in endemic areas be sustained or enhanced. It is also essential that clinicians remain vigilant for the emergence of drug resistance and that research into new drug development continue. The recent experience with tuberculosis should be a lesson in the hazards of complacency and the necessity to maintain a strong control program even when a disease is waning in prevalence.

There is a need for epidemiologic studies to document the extent of the decrease in the prevalence of leprosy and to gather accurate information on the incidence of leprosy. These studies might also help to resolve the uncertainty concerning the mode of transmission of *M leprae*.[6] A rapid decline in disease incidence during an active multidrug therapy-based control program would be consistent with a primary role for human-to-human transmission, whereas a stable or slowly declining incidence might suggest acquisition of *M leprae* infection from the environment. Taken to its logical conclusion, if epidemiologic studies indicate that *M leprae* is simply one of the numerous species of environmental mycobacteria, then simple measures such as providing clean water or shoes for children might be the most cost-effective control strategy.

Progress towards the goal of eradication will also depend on continued support for basic research. There is a desperate need for a diagnostic test that can be done under field conditions by personnel without advanced laboratory or pathology training. As summarized by Gelber, existing serologic tests lack sufficient predictive value for active disease.[6] Preliminary results with assays using the polymerase chain reaction are more promising, but much remains to be done. Improved methods for antimicrobial sensitivity testing would greatly accelerate the process of screening novel compounds for activity against *M leprae* and for detecting drug resistance. Finally, there remains the hope that the growing understanding of the immunology of leprosy will facilitate the design of a vaccine that will consistently produce protective immunity.[7]

These are exciting and optimistic times in the field of leprosy. The work of innumerable researchers and health care professionals is finally beginning to bear fruit, and there is the real possibility of continued dramatic declines in the number of cases. At the same time, it must be remembered that the worldwide epidemic of human immunodeficiency virus infection is placing unprecedented demands on the limited health care budgets of many of the countries where leprosy is highly endemic. The next decade promises to be as exciting and eventful as the one that has just drawn to a close.

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The Enigma of Graves' Ophthalmopathy

AN EXPLANATION FOR THE ASSOCIATION of hyperthyroidism with eye disease has long been sought. In 1835, Robert Graves described the case of a 20-year-old woman with weakness on exertion, weight loss, and tachycardia[1(p36)]:

[T]he eyes assumed a singular appearance, for the eyeballs were apparently enlarged, so that when she slept or tried to shut her eyes, the lids were incapable of closing. When the eyes were open, the white scler[ae] could be seen to a breadth of several lines, all around the cornea. In a few months, the action of the heart continuing with unceasing violence, a tumor of a horseshoe-shape appeared in the front of the throat and exactly in the situation of the thyroid gland.

Although advances have been made in our understanding of Graves' ophthalmopathy since this early description, we still lack the insight needed to design all but essentially palliative therapy for our patients with this disorder.

Investigations concerning the pathogenesis of Graves' ophthalmopathy have been difficult to undertake, largely because there is no animal model for this condition and because of the relative scarcity of affected human orbital tissues available for study. Because the hyperthyroidism of Graves' disease is caused by circulating antibodies directed against a thyroid antigen (the thyroid-stimulating hormone [TSH] receptor), early studies of ophthalmopathy were aimed at detecting autoantibodies directed against orbital antigens. These studies were complicated by the use of porcine tissues by investigators lacking access to human tissues and by the use of crude human tissue preparations that did not allow an exact definition of the cells being studied. Indeed, even today there remains controversy concerning precisely which orbital cell is the target of autoimmune attack in the disease. In addition, it

is unclear whether circulating antibodies reported to be directed against orbital fibroblasts and muscle cells are primarily pathogenic or whether they arise secondarily as a result of the inflammatory process in the orbit.

From a mechanical standpoint, the signs and symptoms of Graves' ophthalmopathy are understood to result from an increase in volume of the soft tissues (connective and muscular) contained within the confines of the bony orbit. The resultant orbital increase in pressure produces forward displacement of the globe and obstruction of venous drainage. These anatomic changes lead to proptosis, periorbital edema, lid edema, chemosis, and conjunctival congestion. Optic neuropathy may be on an ischemic or compressive basis. Early in the disease, the extraocular muscles function poorly due to swelling of the muscle bodies. In late stages of the disease, fibrosis with restriction of these muscles becomes apparent and accounts for their dysfunction.

Many studies have examined the myocyte as a possible target cell in Graves' ophthalmopathy, owing to the massive enlargement of extraocular muscle bodies apparent in tissue specimens and by computed tomographic scanning. Histologic examination of the tissues of the orbit reveals the muscle cells themselves to be intact, however.[2] This has been shown by light and electron microscopy and by electromyography. An accumulation of glycosaminoglycans (GAGs), hydrophilic mucopolysaccharides, is apparent both within the orbital fatty connective tissues in the posterior orbit and within the endomysial connective tissues surrounding the extraocular muscle cells. This accumulation of GAGs, with its attendant edema, results in gross enlargement of the extraocular muscle bodies and swelling of the surrounding orbital connective tissues. Further, histologic examination of pretibial skin biopsy specimens from patients with pretibial dermopathy reveals a similar accumulation of GAGs within the dermal connective tissues.[3] Because GAGs are fibroblast products, the possible role of orbital and pretibial fibroblasts as autoimmune target cells in Graves' disease is of interest. Recent studies have examined the regulation of GAG production by these cells and their potential to express immunomodulatory proteins, such as HLA-DR, intercellular adhesion molecules, and a 72-kilodalton heat-shock protein.[4]

The close clinical association between Graves' hyperthyroidism, ophthalmopathy, and pretibial dermopathy suggests that there may be a common antigen in the thyroid, orbit, and pretibial skin that is recognized by circulating lymphocytes in Graves' disease. Certainly the TSH receptor itself would be a candidate, and recent evidence suggests that fibroblasts might have the ability to express this antigen. The existence, however, of euthyroid Graves' ophthalmopathy, of Graves' hyperthyoidism without clinically detectable ophthalmopathy or pretibial dermopathy, and of apparently unilateral ophthalmopathy is perplexing and must be explained. Several factors are likely involved in the development of the clinical disease, such as variances in orbital anatomy and the presence of many antigenic epitopes. It may be that there is general autoimmune involvement of connective tissue throughout the body in Graves' disease and that regional differences between fibroblasts (such as their abilities to produce particular matrix proteins or to express relevant immunomodulatory proteins) are responsible for the clinical expressions of the disease in the orbit and pretibial skin.

The clinical disease itself has been difficult to study, owing in great part to its diversity of presentation, spectrum of severity, and varied time course of expression. Some patients have severe proptosis with little periorbital edema, whereas others have massive periorbital edema with little proptosis. Still other patients may be bothered primarily by extraocular muscle dysfunction. Further, although clinically notable ophthalmopathy is apparent in only 20% to 40% of patients with Graves' disease, the vast majority of patients can be found to have at least subtle ocular involvement if sensitive imaging techniques are employed. Similarly, although only a few patients with severe ophthalmopathy have pretibial myxedema, histologic examination of the skin of patients with Graves' hyperthyroidism reveals subtle dermatopathic changes in the majority. Thus, Graves' ophthalmopathy and pretibial dermopathy may be considered nearly constant features of Graves' disease, with vastly varied clinical expressions.

Primarily because of the many facets of the clinical expression of Graves' ophthalmopathy, the "no specs" classification of Graves' eye disease was proposed in 1969 and modified in 1977 (Ad Hoc Committee of the American Thyroid Association, Werners Classification). Although this classification system functions well as a teaching device to illustrate the various signs and symptoms of the disease, its use in studies aimed at comparing the results of treatment has tended to obscure the often independent courses of the various components of the disease. Further, the numbered classification suggests that there is a continuous or stepladder progression of the disease, an assumption that does not coincide with clinical observation. The use of the "no specs" classification system to observe a particular patient with the condition is also unsatisfactory for the same reasons. Because of the limitations of this classification system, the International Thyroid Associations have recently urged that this system no longer be used for reporting the results of clinical studies. It is recommended instead that investigators specify the possible benefits of therapy and provide objective data—proptosis measurements, quantitation of extraocular muscle volume and function, measurements of visual acuity, visual fields, color vision—in support of each claim.[5]

In this issue of the journal, William Barrie, MD, presents a comprehensive overview of the diagnosis and management of Graves' ophthalmopathy.[6] He provides a careful and useful discussion of the available treatment options, including the precise symptom or sign of the disease for which each might be indicated. His approach also serves to delineate clinical circumstances in which a patient might best be managed in conjunction with an ophthalmologist, radiotherapist, endocrinologist, or a team of

specialists. Most important, as Barrie points out, each patient requires an individualized approach to management, aiming therapy at those components of the disease that are most troublesome to that particular patient.

There is currently no effective means to prevent ophthalmopathy or to predict which patients with Graves' hyperthyroidism are most likely to go on to have substantial eye disease. Further, because of possible medical side effects and risks inherent in the surgical procedures available, treatment is reserved primarily for patients with advanced, severe disease. While each of these options is useful in particular clinical situations, none specifically addresses basic pathophysiology; corticosteroids, other immunosuppressive agents, and radiotherapy likely function as general immune suppressants, in part by inhibiting the production of cytokines and other inflammatory mediators by activated mononuclear cells. Likewise, transantral surgical decompression of the orbit mechanically relieves the increased pressure within the orbit by allowing the soft tissues to decompress into the maxillary sinus, but does not directly affect the autoimmune process.

The introduction of specific therapeutic and preventive strategies awaits a more complete understanding of the pathogenesis of Graves' ophthalmopathy. For example, therapies directed at neutralizing the stimulators of orbital fibroblast GAG production or modalities that inhibit the expression of immunomodulatory proteins by orbital fibroblasts might be useful. Therapies aimed at earlier steps in the disease process await a delineation of the relevant orbital antigens and of the T-cell epitopes involved. The understanding of basic mechanisms responsible for the association of eye disease, skin disease, and hyperthyroidism will solve a long-perplexing puzzle. More important, it will allow the development of preventive strategies or more effective therapies for our patients with this painful, disfiguring, and sight-threatening disease.

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Is Frequent Marijuana Smoking Harmful to Health?

OVER THE PAST quarter of a century, marijuana has remained the most commonly abused illicit drug in our society. According to the most recent national survey, more than 25% of high school seniors and young adults 19 to 30 years of age in the United States report having used marijuana within the past year, about 15% within the preceding month, and 2.2% to 2.5% (3.2% to 5.3% of young men) daily.[1] These figures probably underestimate the actual prevalence of marijuana smoking, since national surveys underrepresent high-school dropouts and young adults who are difficult to contact by mail, among whom drug use is likely to be greater than among those surveyed. Because smoking is the preferred route of the administration of marijuana and the smoke of marijuana contains a number of respiratory tract irritants and carcinogens,[2] there is justifiable concern that, as with tobacco, the habitual smoking of marijuana over years to decades can produce clinically substantial lung damage and respiratory tract malignancy.

This concern is supported by several experimental studies in animals[3-6] and in vitro[7-9] that have found considerable toxic, inflammatory, and even carcinogenic effects of exposure to marijuana smoke on lung tissue and cells. Until recently, however, few studies have examined the long-term pulmonary effects of real-life heavy, habitual marijuana smoking in humans. Early clinical studies of the respiratory consequences of habitual marijuana smoking published in the mid-1970s yielded conflicting results,[10-13] possibly because of small sample sizes and the failure to control adequately for confounding factors such as concomitant tobacco smoking. A more recent comparison study of 144 heavy, habitual smokers of marijuana only, 135 smokers of marijuana plus tobacco, 70 smokers of tobacco only, and 97 control nonsmokers revealed an association between heavy regular use of marijuana (3 to 4 joints per day for >5 years) and symptoms of acute and chronic bronchitis,[14] dysplastic and inflammatory changes in tracheobronchial mucosa,[15] increased numbers of alveolar macrophages and neutrophils in bronchoalveolar lavage fluid,[16] and impaired microbicidal activity of alveolar macrophages from marijuana smokers compared with tobacco smokers.[17,18] These findings indicate that frequent marijuana smoking can cause airway injury, lung inflammation, and impaired pulmonary defenses against infection. Results of other recent studies, moreover, have documented depressant effects of marijuana components on macrophage and human neutrophil function,[19,20] human natural killer cell activity,[21] and human mononuclear cell cytokine secretion,[22] suggesting that marijuana use increases the susceptibility to infection.

Several lines of evidence suggest that marijuana smoking is also associated with an increased risk for the development of respiratory tract malignancy:

- The insoluble particulate (tar) phase of the smoke from marijuana contains about 50% more of some carcinogenic aryl hydrocarbons, including benz[*a*]anthracene (a weak carcinogen) and benzo[*a*]pyrene (a strong carcinogen), than the smoke from a comparable quantity of unfiltered Kentucky reference tobacco.[2]
- The painting of smoke condensate (tar) from mari-